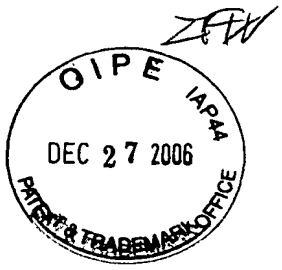
Docket No. 124907-00107




## IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF: Ramachandran THEMBALATH et al. GAU: 1615

SERIAL NO: 10/768,348 EXAMINER: Susan T. Tran

FILED: January 30, 2004

FOR: STABILIZED PAROXETINE HYDROCHLORIDE FORMULATION

## PRIORITY REQUEST

COMMISSIONER FOR PATENTS
P.O. BOX 1450
ALEXANDRIA, VA. 22313-1450

SIR:

☐ Full benefit of the filing date of U.S. Application Serial Number , filed , is claimed pursuant to the provisions of **35 U.S.C. §120**.

☐ Full benefit of the filing date of U.S. Provisional Application Serial Number , filed , is claimed pursuant to the provisions of **35 U.S.C. §119(e)**.

☒ Applicants claim any right to priority from any earlier filed applications to which they may be entitled pursuant to the provisions of **35 U.S.C. §119**, as noted below.

In the matter of the above-identified application for patent, notice is hereby given that the applicants claim as priority:

| COUNTRY | APPLICATION NUMBER | MONTH/DAY/YEAR |
|---|---|---|
| INDIA | PCT/IN03/00349 | 10/31/2003 |
| INDIA | 384/MUM/2003 | 04/17/2003 |
| INDIA | 977/MUM/2003 | 09/18/2003 |

Certified copies of the corresponding Convention Application(s)

☒ are submitted herewith

☐ will be submitted prior to payment of the Final Fee

☐ were filed in prior application Serial No. filed

☐ were submitted to the International Bureau in PCT Application Number .
Receipt of the certified copies by the International Bureau in a timely manner under PCT Rule 17.1(a) has been acknowledged as evidenced by the attached PCT/IB/304.

☐ (A) Application Serial No.(s) were filed in prior application Serial No. filed ; and

(B) Application Serial No.(s)

☐ are submitted herewith

☐ will be submitted prior to payment of the Final Fee

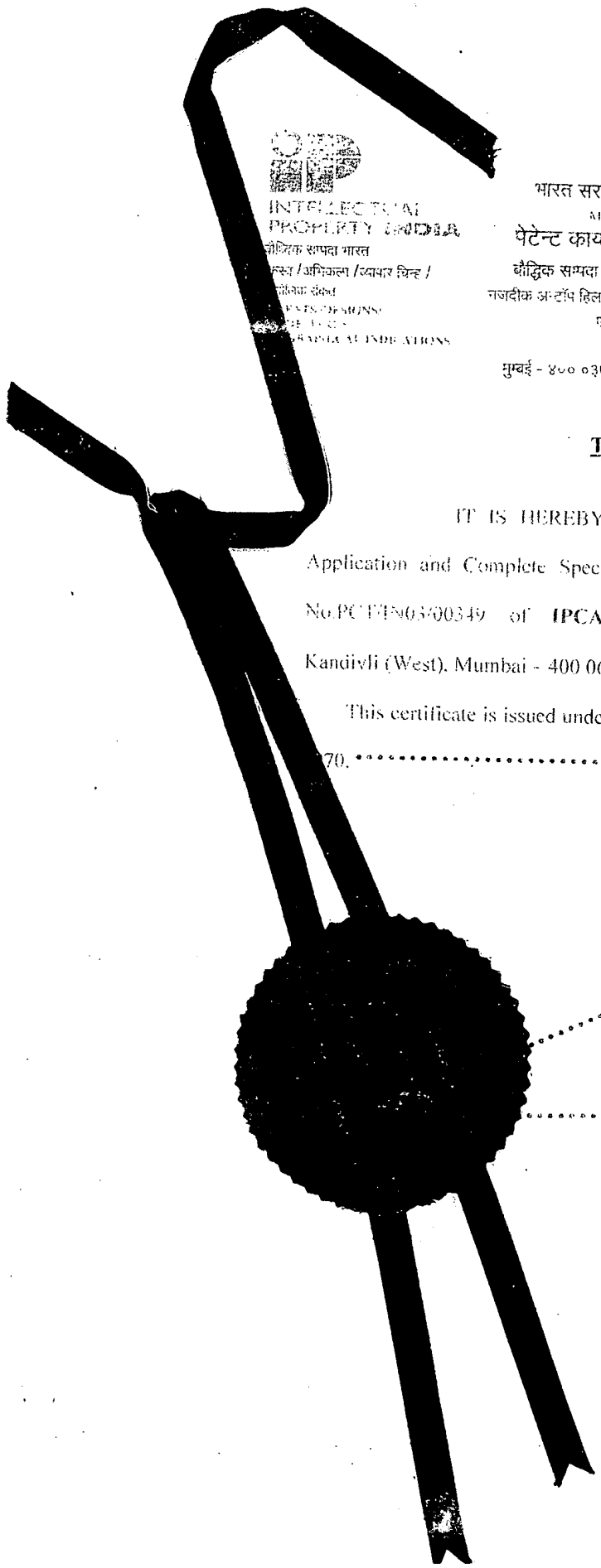
Respectfully Submitted,

BLANK ROME LLP

600 NEW HAMPSHIRE AVENUE, N.W.
WASHINGTON, DC 20037
TEL (202) 944-3000
FAX (202) 572-8398

Brian Wm. Higgins
Registration No. 48,443

Date: December 27, 2006




सत्यमेव जयते

भारत सरकार /Government of India

Ministry Of Commerce & Industry

पेटेन्ट कार्यालय / The Patent Office

बौद्धिक सम्पदा भवन / Boudhik Sampada Bhavan

नजदीक अन्टॉप हिल डाकघर / Near Antop Hill Post Office

एस. एम. रोड / S. M. Road

अन्टॉप हिल / Antop Hill

मुम्बई - ४०० ०३७, भारत,/ Mumbai – 400 037, India

दूरभाष /Tel : 022-2413 7701

फॅक्स / Fax 022-2413 0387

Email: mumbai-patent @nic.in

Website www.ipindia.nic.in


## THE PATENTS ACT, 1970

IT IS HEREBY CERTIFIED THAT, the annex is a true copy of the Patent Application and Complete Specification filed on 31/10/2003 in respect of Patent Application No.PCT/IN03/00349 of **IPCA LABORATORIES LIMITED**, 48, Kandivli Industrial Estate, Kandivli (West), Mumbai - 400 067, Maharashtra, India.

This certificate is issued under the powers vested in me under Section 147 (1) of the Patents Act, 1970.

Dated this 17/5 day of Aug 2006.

M.A. Haafeez

(M.A. HAAFEEZ)

ASSTT.CONTROLLER OF PATENTS & DESIGNS

CERTIFIED COPY OF PRIORITY DOCUMENT

HOME COPY

# PCT

## REQUEST

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty.

For receiving Office use only

PCT / IN 03 / 0 0 3 4 9
International Application No.

31 OCTOBER 2003 ( 3 1. 10. 03 )
International Filing Date

THE PATENT OFFICE, ( INDIA )
PCT INTERNATIONAL APPLICATION
Name of receiving Office and "PCT International Application"

Applicant's or agent's file reference *(if desired) (12 characters maximum)* GNA 603 WO

**Box No. I TITLE OF INVENTION**

PHARMACEUTICAL PREPARATIONS AND PROCESS FOR PRODUCTION THEREOF.

**Box No. II APPLICANT** ☐ This person is also inventor

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

IPCA LABORATORIES LIMITED.
48, Kandivli Industrial Estate,
Kandivli (West), Mumbai - 400 067.
Maharashtra, India.

Telephone No.
+ 91-22-28686097

Facsimile No.
+ 91-22-28688613

Teleprinter No.

Applicant's registration No. with the Office

State *(that is, country)* of nationality: IN

State *(that is, country)* of residence: IN

This person is applicant for the purposes of: ☐ all designated States ☒ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

**Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)**

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

THEMBALATH Ramachandran.
IPCA Laboratories Limited.
48, Kandivli Industrial Estate,
Kandivli (West), Mumbai - 400 067.
Maharashtra, India.

This person is:
☐ applicant only
☐ applicant and inventor
☒ inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office

State *(that is, country)* of nationality: IN

State *(that is, country)* of residence: IN

This person is applicant for the purposes of: ☐ all designated States ☒ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

☒ Further applicants and/or (further) inventors are indicated on a continuation sheet.

**Box No. IV AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE**

The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as: ☒ agent ☐ common representative

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

NAIR Gopakumar G.
Patents & Trademark Agent (Regd.)
Gopakumar Nair Associates,
Nair Baug, Akurli Road,
Kandivli (East), Mumbai - 400 101.

Telephone No.
+ 91-22-28872058

Facsimile No.
+ 91-22-28870856

Teleprinter No.

Agent's registration No. with the Office
IN / PA 509

☐ **Address for correspondence:** Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

Received from I.P.O. on 31/10/03
Vide Entry No. 5382 in the Register of Patents, Bombay.

Form PCT/RO/101 (first sheet) (March 2001; reprint Jan 2004)

*See Notes to the request form*

( 27. 11. 03 )

Sheet No. ...2...

**Continuation of Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)**

*If none of the following sub-boxes is used, this sheet should not be included in the request.*

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

BANSAL Yatish Kumar
IPCA Laboratories Limited
48, Kandivli Industrial Estate,
Kandivli (West), Mumbai - 400 067.
Maharashtra, India

This person is:
- ☐ applicant only
- ☐ applicant and inventor
- ☒ inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office

State *(that is, country)* of nationality: IN

State *(that is, country)* of residence: IN

This person is applicant for the purposes of: ☐ all designated States ☒ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

SINGH Veena.
IPCA Laboratories Limited.
48, Kandivli Industrial Estate,
Kandivli (West), Mumbai - 400 067.
Maharashtra, India

This person is:
- ☐ applicant only
- ☐ applicant and inventor
- ☒ inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office

State *(that is, country)* of nationality: IN

State *(that is, country)* of residence: IN

This person is applicant for the purposes of: ☐ all designated States ☒ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

This person is:
- ☐ applicant only
- ☐ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office

State *(that is, country)* of nationality:

State *(that is, country)* of residence:

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

This person is:
- ☐ applicant only
- ☐ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office

State *(that is, country)* of nationality:

State *(that is, country)* of residence:

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

☐ Further applicants and/or (further) inventors are indicated on another continuation sheet.

**Box No. V DESIGNATION OF STATES** *Mark the applicable check-boxes below; at least one must be marked.*

The following designations are hereby made under Rule 4.9(a):

**Regional Patent**

☒ **AP** **ARIPO Patent:** **GH** Ghana, **GM** Gambia, **KE** Kenya, **LS** Lesotho, **MW** Malawi, **MZ** Mozambique, **SD** Sudan, **SL** Sierra Leone, **SZ** Swaziland, **TZ** United Republic of Tanzania, **UG** Uganda, **ZM** Zambia, **ZW** Zimbabwe, and any other State which is a Contracting State of the Harare Protocol and of the PCT *(if other kind of protection or treatment desired, specify on dotted line)* .....

☒ **EA** **Eurasian Patent:** **AM** Armenia, **AZ** Azerbaijan, **BY** Belarus, **KG** Kyrgyzstan, **KZ** Kazakhstan, **MD** Republic of Moldova, **RU** Russian Federation, **TJ** Tajikistan, **TM** Turkmenistan, and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT

☒ **EP** **European Patent:** **AT** Austria, **BE** Belgium, **BG** Bulgaria, **CH & LI** Switzerland and Liechtenstein, **CY** Cyprus, **CZ** Czech Republic, **DE** Germany, **DK** Denmark, **EE** Estonia, **ES** Spain, **FI** Finland, **FR** France, **GB** United Kingdom, **GR** Greece, **IE** Ireland, **IT** Italy, **LU** Luxembourg, **MC** Monaco, **NL** Netherlands, **PT** Portugal, **SE** Sweden, **SI** Slovenia, **SK** Slovakia, **TR** Turkey, and any other State which is a Contracting State of the European Patent Convention and of the PCT

☒ **OA** **OAPI Patent:** **BF** Burkina Faso, **BJ** Benin, **CF** Central African Republic, **CG** Congo, **CI** Côte d'Ivoire, **CM** Cameroon, **GA** Gabon, **GN** Guinea, **GQ** Equatorial Guinea, **GW** Guinea-Bissau, **ML** Mali, **MR** Mauritania, **NE** Niger, **SN** Senegal, **TD** Chad, **TG** Togo, and any other State which is a member State of OAPI and a Contracting State of the PCT *(if other kind of protection or treatment desired, specify on dotted line)* .....

**National Patent** *(if other kind of protection or treatment desired, specify on dotted line)*:

| | | |
|---|---|---|
| ☒ **AE** United Arab Emirates | ☒ **GM** Gambia | ☒ **NZ** New Zealand |
| ☒ **AG** Antigua and Barbuda | ☒ **HR** Croatia | ☒ **OM** Oman |
| ☒ **AL** Albania | ☒ **HU** Hungary | ☒ **PH** Philippines |
| ☒ **AM** Armenia | ☒ **ID** Indonesia | ☒ **PL** Poland |
| ☒ **AT** Austria | ☒ **IL** Israel | ☒ **PT** Portugal |
| ☒ **AU** Australia | ☐ **IN** India | ☒ **RO** Romania |
| ☒ **AZ** Azerbaijan | ☒ **IS** Iceland | ☒ **RU** Russian Federation |
| ☒ **BA** Bosnia and Herzegovina | ☒ **JP** Japan | |
| ☒ **BB** Barbados | ☒ **KE** Kenya | ☒ **SC** Seychelles |
| ☒ **BG** Bulgaria | ☒ **KG** Kyrgyzstan | ☒ **SD** Sudan |
| ☒ **BR** Brazil | ☒ **KP** Democratic People's Republic of Korea | ☒ **SE** Sweden |
| ☒ **BY** Belarus | | ☒ **SG** Singapore |
| ☒ **BZ** Belize | ☒ **KR** Republic of Korea | ☒ **SK** Slovakia |
| ☒ **CA** Canada | ☒ **KZ** Kazakhstan | ☒ **SL** Sierra Leone |
| ☒ **CH & LI** Switzerland and Liechtenstein | ☒ **LC** Saint Lucia | ☒ **TJ** Tajikistan |
| ☒ **CN** China | ☒ **LK** Sri Lanka | ☒ **TM** Turkmenistan |
| ☒ **CO** Colombia | ☒ **LR** Liberia | ☒ **TN** Tunisia |
| ☒ **CR** Costa Rica | ☒ **LS** Lesotho | ☒ **TR** Turkey |
| ☒ **CU** Cuba | ☒ **LT** Lithuania | ☒ **TT** Trinidad and Tobago |
| ☒ **CZ** Czech Republic | ☒ **LU** Luxembourg | |
| ☒ **DE** Germany | ☒ **LV** Latvia | ☒ **TZ** United Republic of Tanzania |
| ☒ **DK** Denmark | ☒ **MA** Morocco | ☒ **UA** Ukraine |
| ☒ **DM** Dominica | ☒ **MD** Republic of Moldova | ☒ **UG** Uganda |
| ☒ **DZ** Algeria | | ☐ **US** United States of America |
| ☒ **EC** Ecuador | ☒ **MG** Madagascar | |
| ☒ **EE** Estonia | ☒ **MK** The former Yugoslav Republic of Macedonia | ☒ **UZ** Uzbekistan |
| ☒ **ES** Spain | | ☒ **VC** Saint Vincent and the Grenadines |
| ☒ **FI** Finland | ☒ **MN** Mongolia | ☒ **VN** Viet Nam |
| ☒ **GB** United Kingdom | ☒ **MW** Malawi | ☒ **YU** Yugoslavia |
| ☒ **GD** Grenada | ☒ **MX** Mexico | ☒ **ZA** South Africa |
| ☒ **GE** Georgia | ☒ **MZ** Mozambique | ☒ **ZM** Zambia |
| ☒ **GH** Ghana | ☒ **NO** Norway | ☒ **ZW** Zimbabwe |

Check-boxes below reserved for designating States which have become party to the PCT after issuance of this sheet:

| | | |
|---|---|---|
| ☐ ..... | ☐ ..... | ☐ ..... |
| ☐ ..... | ☐ ..... | ☐ ..... |

**Precautionary Designation Statement:** In addition to the designations made above, the applicant also makes under Rule 4.9(b) all other designations which would be permitted under the PCT except any designation(s) indicated in the Supplemental Box as being excluded from the scope of this statement. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit. *(Confirmation (including fees) must reach the receiving Office within the 15-month time limit.)*

**Box No. VI PRIORITY CLAIM**

The priority of the following earlier application(s) is hereby claimed:

| Filing date of earlier application *(day/month/year)* | Number of earlier application | Where earlier application is: | | |
|---|---|---|---|---|
| | | national application: country or Member of WTO | regional application:* regional Office | international application: receiving Office |
| item (1) 17/04/2003 | 384/MUM/2003 | INDIA | MUMBAI | |
| item (2) | | | | |
| item (3) | | | | |
| item (4) | | | | |
| item (5) | | | | |

☐ Further priority claims are indicated in the Supplemental Box.

The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) *(only if the earlier application was filed with the Office which for the purposes of this international application is the receiving Office)* identified above as:

☐ all items ☒ item (1) ☐ item (2) ☐ item (3) ☐ item (4) ☐ item (5) ☐ other, see Supplemental Box

** Where the earlier application is an ARIPO application, indicate at least one country party to the Paris Convention for the Protection of Industrial Property or one Member of the World Trade Organization for which that earlier application was filed (Rule 4.10(b)(ii)):* ....

**Box No. VII INTERNATIONAL SEARCHING AUTHORITY**

**Choice of International Searching Authority (ISA)** *(if two or more International Searching Authorities are competent to carry out the international search, indicate the Authority chosen; the two-letter code may be used)*:

ISA / AT

**Request to use results of earlier search; reference to that search** *(if an earlier search has been carried out by or requested from the International Searching Authority)*:

Date *(day/month/year)* Number Country *(or regional Office)*

**Box No. VIII DECLARATIONS**

The following **declarations** are contained in Boxes Nos. VIII (i) to (v) *(mark the applicable check-boxes below and indicate in the right column the number of each type of declaration)*: Number of declarations

| | | | |
|---|---|---|---|
| ☐ | Box No. VIII (i) | Declaration as to the identity of the inventor | : |
| ☒ | Box No. VIII (ii) | Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent | : |
| ☒ | Box No. VIII (iii) | Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application | : |
| ☐ | Box No. VIII (iv) | Declaration of inventorship (only for the purposes of the designation of the United States of America) | : |
| ☐ | Box No. VIII (v) | Declaration as to non-prejudicial disclosures or exceptions to lack of novelty | : |

**Box No. VIII (ii) DECLARATION: ENTITLEMENT TO APPLY FOR AND BE GRANTED A PATENT**

*The declaration must conform to the standardized wording provided for in Section 212; see Notes to Boxes Nos. VIII, VIII (i) to (v) (in general) and the specific Notes to Box No. VIII (ii). If this Box is not used, this sheet should not be included in the request.*

Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent (Rules 4.17(ii) and 51*bis*.1(a)(ii)), in a case where the declaration under Rule 4.17(iv) is not appropriate:

In relation to this application IPCA Laboratories Limited is entitled as employer of the inventors and the inventors have assigned the invention to M/s IPCA Laboratories Limited.

THEMBALATH Ramachandran

BANSAL Yatish Kumar

SINGH Veena

This declaration is made for the purposes of all designations except the designation of the United States of America.

For IPCA Laboratories Limited

THEMBALATH Ramachandran
Executive Director

☐ This declaration is continued on the following sheet, "Continuation of Box No. VIII (ii)".

( 2 7. 11. 03 )



**Box No. VIII (iii) DECLARATION: ENTITLEMENT TO CLAIM PRIORITY**

*The declaration must conform to the standardized wording provided for in Section 213; see Notes to Boxes Nos. VIII, VIII (i) to (v) (in general) and the specific Notes to Box No. VIII (iii). If this Box is not used, this sheet should not be included in the request.*

Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application specified below, where the applicant is not the applicant who filed the earlier application or where the applicant's name has changed since the filing of the earlier application (Rules 4.17(iii) and 51*bis*.1(a)(iii)):

We hereby declare that the priority application number 384/MUM/2003 as well as the current PCT application have both have been filed by one and the same applicant namely,

IPCA Laboratories Limited
48, Kandivli Industrial Estate,
Kandivli (West), Mumbai - 400 067.
Maharashtra, India.

We further declare that the agent for the applicant in the priority application number 384/MUM/2003 as well as the current PCT application is one and the same agent namely,

NAIR Gopakumar G.
Gopakumar Nair Associates
(Regd. Patent Agent - Reg. No. IN / PA 509)

For IPCA Laboratories Limited

THEMBALATH Ramachandran
Executive Director

☐ This declaration is continued on the following sheet, "Continuation of Box No. VIII (iii)".

**Box No. IX CHECK LIST; LANGUAGE OF FILING**

This international application **contains**:

(a) **in paper form**, the following number of sheets :

| | | |
|---|---|---|
| request (including declaration sheets) | : | 7 |
| description (excluding sequence listings and/or tables related thereto) | : | 13 |
| claims | : | 4 |
| abstract | : | 1 |
| drawings | : | |
| **Sub-total number of sheets** | : | 25 |
| sequence listings | : | |
| tables related thereto | : | |
| *(for both, actual number of sheets if filed in paper form, whether or not also filed in computer readable form; see (c) below)* | | |
| **Total number of sheets** | : | 25 |

(b) ☐ **only in computer readable form** (Section 801(a)(i))
- (i) ☐ sequence listings
- (ii) ☐ tables related thereto

(c) ☐ **also in computer readable form** (Section 801(a)(ii))
- (i) ☐ sequence listings
- (ii) ☐ tables related thereto

**Type and number of carriers** (diskette, CD-ROM, CD-R or other) on which are contained the
- ☐ sequence listings: . . . . . .
- ☐ tables related thereto: . . . . . .

*(additional copies to be indicated under items 9(ii) and/or 10(ii), in right column)*

This international application is **accompanied by** the following item(s) *(mark the applicable check-boxes below and indicate in right column the number of each item)*: — Number of items

1. ☐ fee calculation sheet :
2. ☒ original separate power of attorney :
3. ☐ original general power of attorney :
4. ☐ copy of general power of attorney; reference number, if any: . . . . . :
5. ☐ statement explaining lack of signature :
6. ☐ priority document(s) identified in Box No. VI as item(s): . . . . . :
7. ☐ translation of international application into *(language)*: . . . . . :
8. ☐ separate indications concerning deposited microorganism or other biological material :
9. ☐ sequence listings in computer readable form *(indicate type and number of carriers)*
   - (i) ☐ copy submitted for the purposes of international search under Rule 13*ter* only (and not as part of the international application) :
   - (ii) ☐ *(only where check-box (b)(i) or (c)(i) is marked in left column)* additional copies including, where applicable, the copy for the purposes of international search under Rule 13*ter* :
   - (iii) ☐ together with relevant statement as to the identity of the copy or copies with the sequence listings mentioned in left column :
10. ☐ tables in computer readable form related to sequence listings *(indicate type and number of carriers)*
    - (i) ☐ copy submitted for the purposes of international search under Section 802(b-*quater*) only (and not as part of the international application) :
    - (ii) ☐ *(only where check-box (b)(ii) or (c)(ii) is marked in left column)* additional copies including, where applicable, the copy for the purposes of international search under Section 802(b-*quater*) :
    - (iii) ☐ together with relevant statement as to the identity of the copy or copies with the tables mentioned in left column :
11. ☐ other *(specify)*: . . . . . :

**Figure of the drawings** which should accompany the abstract:

**Language of filing** of the international application: English

**Box No. X SIGNATURE OF APPLICANT, AGENT OR COMMON REPRESENTATIVE**

*Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the request).*

NAIR Gopakumar G.
Regd. Patent Agent
(Regd. No. IN / PA 509)

For receiving Office use only

1. Date of actual receipt of the purported international application: 31 OCTOBER 2003 ( 31.10.03 )
2. Drawings: ☐ received: ☐ not received:
3. Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application:
4. Date of timely receipt of the required corrections under PCT Article 11(2):
5. International Searching Authority (if two or more are competent): ISA /
6. ☐ Transmittal of search copy delayed until search fee is paid

For International Bureau use only

Date of receipt of the record copy by the International Bureau:

# PHARMACEUTICAL PREPARATIONS AND PROCESS FOR PRODUCTION THEREOF

**Related Application**

This application claims priority from India National patent application serial No. 384/MUM/2003, filed 17th April 03.

**Field of the Invention**

This invention relates to novel pharmaceutical preparations and a process of production thereof. More specifically, the invention relates to a novel process of preparing a stabilized oral dosage form of an active pharmaceutical ingredient (API) such as paroxetine hydrochloride and a novel process for improving the stability of the said active pharmaceutical ingredient (API) prior to incorporating into an oral delivery system. This invention further relates to a process for preparation of free flowing granules of paroxetine hydrochloride obtained by coating them with moisture barrier pharmaceutical excipients. More specifically, this invention relates to the process for the preparation of coated granules of paroxetine hydrochloride anhydrate and oral pharmaceutical compositions containing the same.

**Background and Prior Art**

Paroxetine is chemically described as (-)-trans-4-((4'-flurophenyl)3-3(3'4'-Methylenedioxy phenoxy methyl) - piperidine. Paroxetine has been approved for treating depression in humans.

Paroxetine (API) has first been claimed for its antidepressant properties in US Pat 3,912,743 and US 4007196 (Ferrosan, Denmark). In 1980 paroxetine was licensed to Smithkline, where paroxetine was described as the maleate salt.

Crystalline paroxetine hydrochloride hemihydrate, process for its preparation, compositions containing the same and its preparation, and its therapeutic use as antidepressant has been claimed in US Pat.4721723 and EP 223403.

Thereafter, a large number of patent applications have been filed and patents granted for different forms of the API different pharmaceutical formulations using paroxetine and processes for formulating the same.

Patent WO9958113 describes paroxetine hydrochloride used in amorphous form or in the form of a crystalline anhydrate which is formulated into tablets under conditions such that there is no detectable conversion to hemihydrate during the tabletting process. Such conditions have been achieved by the use of essentially anhydrous or low moisture

excipients such as dibasic calcium phosphate anhydrous (A_TAB*), anhydrous direct compression lactose, monosachharide sugars e.g.mannitol, disaccharide sugars e.g. lactitol (Finlac DC*), powdered cellulose, pregelatinised starch, microcrystalline cellulose (Avicel PH112*), sodium starch glycolate, croscarmellose sodium(Ac-Di-SolF*),colloidal silicon dioxide (Syloid 244*) (Explotab*), magnesium stearate and talc. Paroxetine hydrochloride anhydrate is mixed with the anhydrous or low moisture excipients and compressed using standard pharmaceutical procedures. As an additional aid to the protection of this product from the deleterious affects of moisture, the tablets are film- coated using hydrophobic coating materials such as glyceryl behenate (Compitrol 888*) using a hot melt coating technique.

Patent WO9958116 uses the same API and excipients for a capsule formulation i.e. paroxetine hydrochloride anhydrate is mixed with anhydrous or low moisture excipients and filled into cellulose capsule shell of intrinsically low moisture content (e.g. Shiono Qualicaps). The invention also finds that dibasic calcium phosphate anhydrous and polyglycolized glycerides can be used to form oral swallow capsules with paroxetine anhydrate without undesired conversion to hemihydrate during manufacturing process.

Patent WO02102382 describes a process for preparing paroxetine hydrochloride from paroxetine base which provides paroxetine hydrochloride substantially free of pink-colored compounds or an impurity identified by an HPLC RRT of about 1.5.

US Patent. No. 5,955,475 describes an invention where paroxetine free base is formulated into pharmaceutical compositions when adsorbed on or absorbed by a solid carrier.

Patent WO 9831365 elaborates a process for preparing a free flowing form of paroxetine hydrochloride which comprises spray drying a solution of paroxetine hydrochloride. However no discussion appears in the patent regarding the problem of colour development.

US Patent No. 6168805 discloses an invention that relates to a process for preparing solid, amorphous paroxetine comprising a) mixing paroxetine free base or its salt with water and a pharmaceutically acceptable polymer and b) drying to form a composition comprising amorphous paroxetine and polymer, eliminating the need for organic solvents common for the solvent process. The resultant amorphous solid paroxetine composition is free from crystalline form and yet has good handling properties, making it suitable for pharmaceutical use in the traditional tablet dosage form.

Patent WO0102393 complexes of paroxetine, as free base or salt, with cyclodextrin or a cyclodextrin derivative show a high chemical stability, an improved solubility in water and are suitable for the preparation of liquid or solid pharmaceutical compositions.

Patent WO9948499 paroxetine free base is advantageously formulated into pharmaceutical compositions when adsorbed on or absorbed by a solid carrier. The composition of this

invention is simply obtained by combining a solution of paroxetine with a suitable adsorbent or absorbent material and evaporating the solvent, for example by spray drying.

US patent No. 6503927 describes a stable amorphous paroxetine hydrochloride composition employing an aqueous solvent medium containing an acidulant and polyvinylpyrrolidone and drying the resulting solid dispersion. The preferred compositions include amorphous paroxetine hydrochloride, polyvinylpyrrolidone and citric acid.

WO9926625 provides pharmaceutical formulations of paroxetine in which paroxetine is in solution in a solid, semi-solid or liquid carrier. The solutions are used to fill capsules, or self-supporting solid solutions are shaped into solid dosage forms such as tablets or pellets.

Patent WO 95/16448 reveals that earlier commercial paroxetine hydrochloride hemihydrate tablets were made using a wet granulation process. Further, the commercial tablets exhibited a colour change i.e. the tablets developed a pink hue that is undesirable.

Patent US2002065301 elaborates paroxetine salt compositions made with the aid of water by controlling the pH to 6.5 or less. These compositions have improved stability without significant coloration problems. The paroxetine salts include paroxetine hydrochloride salts but preferably use paroxetine sulfonate salts such as paroxetine methane sulfonate.

US Patent 6113944 relates paroxetine which is formulated into tablets using a formulation process in which water is absent. Direct Compression technique has been used where paroxetine hydrochloride hemihydrate is conventionally admixed with dry excipients and compressed into tablets or by dry granulation techniques as in US Patent No. 6007842 where paroxetine hydrochloride hemihydrate is conventionally admixed with dry excipients and compressed into large slugs or roller compacted into ribbon- like strands. The compacted material is then suitably milled to produce a free flowing powder which is then compressed into tablets. The excipients revealed in the patent include dicalcium phosphate dihydrate (Emcompress* or Ditab*), microcrystalline cellulose (Avicel PH 102*), sodium starch glycollate (Explotab*) & magnesium stearate.

**Summary of the Invention**

In the present invention, we have provided a novel pharmaceutical preparation and a process for production thereof, the active pharmaceutical ingredient being formulated with a protective coating prior to incorporating into the dosage form. We have thereby substantially eliminated the possibility of degradation or color development by accelerated stability studies and have introduced characteristics of stability into the solid oral dosage form.

In accordance with the present invention, there is provided a substantially moisture stable pharmaceutical preparation in the form of a solid oral dose comprising;

(a) an active core comprising a granulated pharmaceutically active ingredient; and

(b) a moisture barrier coating enveloping individual granules of the active core.

Preferably, the moisture barrier coating permeates the active core, enveloping individual granules of the core. Even more preferably, granules in the region of the center of the active core are surrounded with and contacted by the moisture barrier coating.

Accordingly, the invention provides a substantially moisture stable pharmaceutical preparation in the form of a solid oral dose comprising;

(a) an active core comprising a granulated pharmaceutically active ingredient; and

(b) a barrier coating surrounding the active core comprising a moisture barrier agent dispersed in an organic solvent.

"Substantially moisture stable" means that the preparation has the ability to retard degradation by means of water.

The usage of ethylcellulose provided a hydrophobic coating to the active and improved the stability of the product by inhibiting oxidation. Ethylcellulose additionally worked as a binder in the formulation. Granules coated with ethylcellulose demonstrated the added advantage of ability to absorb compression pressure and hence protect the coating from breaking during compression.

Coated granules of paroxetine hydrochloride anhydrate are disclosed which are prepared using a solution of moisture barrier excipient and a nonionic surfactant in an organic solvent. Such granules are manufactured by preparing a semisolid mass of the API and the solution of moisture barrier coating, preparing strands of suitable diameter of the wet mass, drying the strands and finally milling to get granules of desired size. The granules of the API are then incorporated into solid oral dose formulations of paroxetine. Alternately the coating of powder is obtained by coating fluidized API in a suitable equipment.

In accordance with a further aspect of the present invention, there is provided a process for producing a substantially moisture stable pharmaceutical preparation in the form of a solid oral dose as described hereinabove comprising the steps of:

(a) granulated a pharmaceutically active ingredient to form a granulated active core;

(b) coating the individual granules of the active core with a barrier coating comprising a moisture barrier agent; and

(c) forming the coated granules into a solid oral dose.

Thus, the invention provides a process for producing a substantially moisture stable pharmaceutical preparation in the form of a solid oral dose comprising the steps:

(a) granulated a pharmaceutically active ingredient to form an active core ; and

(b) coating the active core with a barrier coating comprising a moisture barrier agent dispersed in an organic solvent.

**Detailed Description**

In keeping with our objective of providing long term stability to the oral solid dosage form of paroxetine hydrochloride, we have selected excipients which would contribute to this characteristic objective. We have chosen not to use excipients such as disaccharides such as maltose, lactose, sucrose and glucose. Solvents like water or any other aqueous solvent or solvents that are freely miscible with water have also not been used.

We have also considered a coating agent which would provide excellent protection against moisture and at the same time immediately release the drug in the gastro-intestinal environment, as desired.

Paroxetine hydrochloride anhydrous has been chosen for experimental trials since it is considered more difficult to protect from moisture. It is also an aspect of the present invention to provide a pharmaceutical composition incorporating paroxetine hydrochloride hemihydrate by using the process herein above.

The process has also provided positive results with regard to other moisture barrier excipients such as polyethylene glycols, polyglycolised glycerides, fatty alcohols, stearic acid, opadry AMB OY-B-28920 white and Opadry 20A 58900 white, fatty materials of plant and animal origin. Additionally the tablets may also be film coated with hydrophobic coating materials to help retard against degradation.

The following examples illustrate the various aspects of the present invention.

**EXAMPLE 1**

A coating solution of ethylcellulose was produced to dissolve in methylene chloride and iso-propyl alcohol. Polysorbate was added to this solution. The active was coated with this coating solution. The coated granules formed were dried at a suitable temperature and screened through a mesh of appropriate size. Dicalcium phosphate, microcrystalline cellulose and sodium starch glycollate were milled to which milled citric acid was geometrically mixed. Finally the dried mass of coated active granules were sized appropriately and blended with the above mixture and lubricated with the help of magnesium stearate. These resultant granules could be adequately compressed to tablets or could be suitably filled into hard gelatin capsule shells.

The pharmaceutical composition of the tablets containing paroxetine hydrochloride anhydrous has the following composition.

| | |
|---|---|
| Paroxetine hydrochloride anhydrous | 33.32 mg |
| Polysorbate 80 | 2.00 mg |
| Ethylcellulose (10 cps) | 0.33 mg |
| Acetone; Isopropyl alcohol | 1: 3 ratio |
| Dicalcium phosphate (dihydrate granular) | 320.35 mg |
| Microcrystalline cellulose (Avicel PH 102) | 100.00 mg |
| Sodium starch glycollate (Primogel) | 20.00 mg |
| Citric acid | 4.00 mg |
| Magnesium sterate | 5.00 mg |

**EXAMPLE 2**

The moisture retardant coated active pharmaceutical ingredient was prepared by Fluid Bed Processor (GLATT).

Ethyl cellulose was dissolved in the solvent mixture of methylene chloride and isopropyl alcohol. Complete dissolution was ensured and then polysorbate 80 was added to the solution and mixed avoiding foaming.

The bowl of the Fluid bed processor (FBP) was loaded with paroxetine hydrochloride anhydrate. The API was fluidized in the FBP and coating solution sprayed through the spray

nozzle till granulation point was reached which was confirmed at the entrance port on the exterior of the expansion chamber.

- Inlet temp. 60 ° C- 80 ° C
- Product temp. 30°c - 45° C
- Flap opening 25% - 50%
- Spray rate 10% - 20 %
- Atomising air NLT 2.5 Kg/cm2 pressure

(iv) The granules were dried to a desired moisture content of NMT 1%

(v) Dicalcium phosphate (dihydrate granular) was added, microcrystalline cellulose (Avicel pH 102), sodium starch glycollate (Primogel), milled citric acid anhydrous and fluidised. Magnesium sterate was added and further fluidized.

(vi) The blend was compressed into tablets using suitable punches.

(vii) The tablets are aqueous film coated using HPMC

**EXAMPLE 3**

Alternately, the active ingredient was coated by a moisture barrier solution and granulated by Rapid Mixer Granulator (RMG).

(i) Coating solution preparation

Ethyl cellulose was dissolved in the solvent mixture of methylene chloride and isopropyl alcohol. Complete dissolution was ensured and polysorbate 80 was added in the solution and mixed avoiding foaming.

(ii) The bowl of the Rapid Mixer Granulator (RMG) was loaded with paroxetine hydrochloride anhydrate. The mixer was started at low speed. The coating solution was poured on the bed of the paroxetine hydrochloride powder and mixed till a wet mass was obtained. The wet mass was sized using suitable screens.

(iii) The granules were dried in a fluid bed drier with the following parameters till the moisture content of NMT 1%

- Inlet temp. 60° C- 70° C
- Product temp. 30°C - 45° C

(iv) Dicalcium phosphate (dihydrate garnular), microcrystalline cellulose (Avicel pH 102), sodium starch glycollate (Primogel) and citric acid anhydrous were added and mixed in a double cone blender. Magnesium sterate was added and mixed thereafter.

(v) The resultant blend was compressed into tablets using suitable punches.

(vi) The tablets were aqueous film coated using HPMC

Although this invention has been described with reference to specific embodiments thereof, it is to be understood that other embodiments and variations of the inventions as described and exemplified may be made by those skilled in the art without departing from the true spirit of invention. It is intended that the appended claims be construed to include all such embodiments and variations.

**CLAIMS**

1. A substantially moisture stable pharmaceutical preparation in the form of a solid oral dose comprising;

   (c) an active core comprising a granulated pharmaceutically active ingredient; and

   (d) a moisture barrier coating enveloping individual granules of the active core.

2. A pharmaceutical preparation as claimed in claim 1, wherein the moisture barrier coating permeates the active core, enveloping individual granules of the core.

3. A pharmaceutical composition according to claim 2, wherein granules in the region of the center of the active core are surrounded with and contacted by the moisture barrier coating.

4. A pharmaceutical preparation as claimed in claim any preceding claim, wherein the active pharmaceutical ingredient is paroxetine hydrochloride anhydrate or paroxetine hydrochloride hemihydrate.

5. A pharmaceutical preparation as claimed in any preceding claim, wherein the barrier coating is hydrophobic.

6. A pharmaceutical preparation as claimed in any preceding claim, wherein the barrier coating further comprises a nonionic surfactant.

7. A pharmaceutical preparation as claimed in any preceding claim, wherein the barrier coating comprises a moisture barrier agent selected from one or more of the following agents: ethyl cellulose, polyethylene glycols, polyglycolised glycerides, fatty alcohols,

stearic acid, opadry AMB OY-B-28920 white and Opadry 20A 58900 white and fatty materials of plant and animal origin.

8. A pharmaceutical preparation as claimed in any preceding claim, incorporating anhydrous citric acid for pH related stability adjustment.
9. A pharmaceutical preparation as claimed in any preceding claim, further comprising one or more of the following ingredients: a diluent, a disintegrant and a lubricant.
10. A pharmaceutical preparation as claimed in claim 9, wherein dibasic calcium phosphate or microcrystalline cellulose is used as a diluent.
11. A pharmaceutical preparation as claimed in any one of claims 8 to 10, wherein sodium starch glycollate is used as a disintegrant.
12. A pharmaceutical preparation as claimed in any of claims 8 to 11, wherein magnesium stearate is used as a lubricant.
13. A pharmaceutical preparation as claimed in preceding claim, wherein the preparation is in the form of a tablet or the preparation is placed within a capsule.
14. A pharmaceutical preparation as claimed in claim 13, wherein the tablet is caplet shaped.
15. A pharmaceutical preparation as claimed claim 13 or claim 14, wherein the granules are compressed into tablets with hardness ranging from 150- 200 Norton
16. A pharmaceutical preparation as claimed in any of claims 13 to 15, wherein the tablets are optionally further coated with conventional film coating materials.
17. A pharmaceutical preparation as claimed claim 16, wherein the film coating is a hydrophobic material.

18. A pharmaceutical preparation as claimed in any preceding claim, wherein the pharmaceutical preparation is substantially resistant to moisture-degradation of the active ingredient and/or the development of pink hue.

19. A pharmaceutical preparation as claimed in any preceding claim, wherein the pharmaceutical preparation further comprises pharmaceutically acceptable excipients in order to mask the taste of the preparation.

20. A pharmaceutical preparation as claimed in any of claims 11 to 12 and 17 to 18, wherein the preparation is placed into hard gelatin capsules

21. A process for producing a substantially moisture stable pharmaceutical preparation in the form of a solid oral dose as described in any one of claims 1 to 19 comprising the steps of:

(d) granulated a pharmaceutically active ingredient to form a granulated active core;

(e) coating the individual granules of the active core with a barrier coating comprising a moisture barrier agent; and

(f) forming the coated granules into a solid oral dose.

22. A process according to claim 21, wherein the coating is achieved by contacting individual granules of the active core with a solution of the moisture barrier agent in an organic solvent.

23. A procees according to claim 22, wherein the contacted granules are dried to remove the organic solvent and provide individual coated granules.

24. A process according to claim 22 or claim 23 wherein the organic solvent is selected from methylene chloride, isopropyl alcohol, acetone and mixtures of one or more thereof.

25. A process according to claim 24, wherein Polysorbate 80 is added to the organic solvent.

## ABSTRACT

This invention describes novel pharmaceutical preparations and a process of production thereof. It is preferred that the preparation comprises a stabilized oral dosage form of an active pharmaceutical ingredient (API) such as paroxetine hydrochloride for improving the stability of the said active pharmaceutical ingredient (API) prior to incorporating into an oral delivery system. This invention further relates to a process for preparation of free flowing granules of paroxetine hydrochloride obtained by coating them with moisture barrier pharmaceutical excipients. More specifically, this invention relates to the process for the preparation of coated granules of paroxetine hydrochloride anhydrate and oral pharmaceutical compositions containing the same.